General

Guideline Title

Effectiveness of practices to increase timeliness of providing targeted therapy for inpatients with bloodstream infections: a Laboratory Medicine Best Practices systematic review and meta-analysis.

Bibliographic Source(s)

Buehler SS, Madison B, Snyder SR, Derzon JH, Cornish NE, Saubolle MA, Weissfeld AS, Weinstein MP, Liebow EB, Wolk DM. Effectiveness of practices to increase timeliness of providing targeted therapy for inpatients with bloodstream infections: a Laboratory Medicine Best Practices systematic review and meta-analysis. Clin Microbiol Rev. 2016 Jan;29(1):59-103. [81 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the ratings of overall strength of evidence and recommendation categories are provided at the end of the "Major Recommendations" field.

Conclusions and Recommendation

On the basis of low overall strength of evidence of effectiveness, no recommendation is made for or against the use of the three assessed practices of this review due to insufficient evidence; however, the overall strength of evidence is simply classified as suggestive due to the fact that most studies received a fair study quality rating. Despite there being no firm recommendation, the data do suggest that each of these three practices has the potential to improve times to initiate targeted therapy and possibly improve other patient outcomes.

The findings of effectiveness are based on three published and two unpublished studies for rapid molecular techniques without additional direct communication, four published and three unpublished studies on rapid molecular techniques with additional direct communication, and four published studies on rapid phenotypic techniques with additional direct communication. A number of the unpublished studies have since been published and are listed in the references (see the original guideline document). Of the 16 included studies, 2 were rated to be of poor quality and thus not used to determine recommendations; only 3 were rated as being of good quality for estimating the results most relevant to the review question, and 11 were rated as fair. Of the 14 studies of fair or good quality, most, 10 total, were judged to have substantial effect sizes for improving outcomes, while 3 were judged to have a moderate effect size, and 1 had an effect size ranked as minimal to none. For both practices involving rapid molecular techniques, the low strength of evidence is based on inconsistent findings (attributable to one study) and the overall lack of studies determined to be of good quality. Though the evidence was consistent for the practice of using phenotypic techniques with additional direct communication in improving outcomes, none of the four studies were rated as being of good quality and did not provide sufficient evidence supporting this practice.

The average standard difference in means for the three practices was as follows: −0.396 (95% confidence interval [CI], −0.888 to 0.44; not significant) for rapid molecular techniques; −1.483 (95% CI, −2.691 to -0.275; $P<0.05$) for rapid molecular techniques, with additional direct communication; and −0.175 (95% CI, −0.279 to −0.072; $P<0.05$) for phenotypic techniques, with additional direct communication. Standard differences in means less than zero favor the rapid test practice over the comparator practice. The meta-analysis results suggest that the implementation of any of the three practices may be more effective at increasing timeliness to targeted therapy than routine microbiology techniques for identification of the microorganisms causing bloodstream infections (BSIs). Based on the included studies, results for all three practices appear applicable across multiple microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), *S. aureus*, *Candida* species, and *Enterococcus* species.

In conclusion, this article is a systematic review of the effectiveness of three rapid diagnostic practices for improving the timeliness of targeted therapy in patients with BSIs: rapid molecular techniques without additional direct communication, rapid molecular techniques with additional direct communication, and rapid phenotypic techniques with additional direct communication. The Centers for Disease Control and Prevention (CDC)-funded Laboratory Medicine Best Practices initiative systematic review methods for quality improvement practices were used. Fourteen studies met review inclusion criteria. Three were rated as being of good quality, and 11 were rated as fair. Most studies had substantial effect size ratings. The average standard difference in means for the three practices compared to more routinely performed practices favored the rapid test practice. However, because most studies were of only fair quality, the overall strength of evidence of effectiveness is only suggestive for each of the three practices in improving timeliness for targeted therapy in patients hospitalized with BSIs. Therefore, the authors are unable to make a recommendation for or against the three practices evaluated due to insufficient evidence. To create a more robust evidence base, a suggested roadmap for future studies is provided for use in preparing existing data or performing a prospective study for submission and effectiveness analysis for these practices (see Appendix 6 in the original guideline document).

Definitions

Overall Strength of Evidence Ratings*

The Expert Panel rates the overall strength of the body of evidence in support of the practice and it is categorized as High, Moderate, Suggestive, and Insufficient as defined.

High: Adequate volume of consistent evidence of substantial healthcare quality impact from studies without major limitations.

Moderate: Some evidence of consistent substantial healthcare quality impact from studies without major limitations; OR an adequate volume of consistent evidence of moderate healthcare quality impact from studies without major limitations.

Suggestive: Limited evidence of moderate healthcare quality impact from a small number of studies without major limitations; OR the quality of some studies' design and/or conduct is limited.

Insufficient: Any estimate of an effect on healthcare quality impact is too uncertain.

*These rating categories have their basis in the work of Guyatt et al.; they were modified to reflect both the quality of the evidence and effect size observed, rather than attempting to anticipate the impact of future potential evidence. The modified definitions for these categories are modeled after the U.S. Preventive Services Task Force.

Recommendation Categories

Recommend: High or moderate for improving healthcare quality. The practice should be identified as a "best practice" for implementation in appropriate care settings, taking into account variations and applicability in implementation and/or care settings.

No recommendation for or against: Suggestive or insufficient. A potentially favorable impact on healthcare quality is not of sufficient size, or not sufficiently supported by evidence to indicate that it should be identified as a "best practice" for implementation in appropriate care settings.

Recommend against: High or moderate for adversely affecting healthcare quality. The practice should not be identified as a "best practice" for implementation because it is not likely to result in more good than harm.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Bloodstream infections

Guideline Category

Diagnosis

Technology Assessment

Clinical Specialty

Critical Care

Infectious Diseases

Internal Medicine

Pathology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Clinical Laboratory Personnel

Hospitals

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the evidence for the effectiveness of three rapid diagnostic practices in decreasing the time to targeted therapy for hospitalized patients with bloodstream infections (BSIs)

Target Population

All hospital inpatients who have a bloodstream infection (BSI)

Interventions and Practices Considered

1. Rapid molecular techniques, with additional direct communication of test results to clinicians or pharmacists
2. Rapid molecular techniques without additional direct communication of test results (i.e., with only routine communication via an electronic medical record)

3. Rapid phenotypic techniques with additional direct communication of test results to clinicians or pharmacists
4. Rapid phenotypic technique, with no additional direct communication
5. Rapid Gram stain

Note: No recommendations could be made for any of the above practices because of low overall strength of evidence. Point-of-care tests, generally defined as those delivering results within ≤20 to 30 minutes of specimen collection, were not included, and notably, none existed for bloodstream infections at the time of the review or at the time of this publication. Rapid methods for mass spectrometry were originally included in the literature review but were excluded when none were identified by 2011.

Major Outcomes Considered

- Time to targeted therapy
- Mortality
- Morbidity
- Hospital lengths of stay
- Antibiotic use
- Cost of care

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The question to be answered by this evidence review is, "for hospital inpatients who are admitted for, or found to have, bloodstream infections (BSIs) (e.g., positive blood cultures), what practices are effective at increasing the timeliness of providing targeted therapy?" This review question is addressed in the context of the BSI analytic framework depicted in Figure 1 in the original guideline document. The relevant population, intervention, comparison, and outcome (PICO) elements are as follows:

- Population: all hospital inpatients who have a BSI
- Interventions:
  - Rapid molecular technique, with additional direct communication
  - Rapid molecular technique, with no additional direct communication
  - Rapid phenotypic technique, with additional direct communication
  - Rapid phenotypic technique, with no additional direct communication
  - Rapid Gram stain
- Comparison: Conventional microbiology testing with phenotypic biochemical or antigenic methods
- Outcomes:
  - Time to targeted therapy is the primary outcome of interest
  - Secondary outcomes (as described in the original guideline document; see also the "Major Outcomes" field in this summary)

Literature Search and Request for Unpublished Studies

A comprehensive literature search was conducted to identify studies with measurable outcomes. With input from the expert panel and the assistance of a research librarian, a literature search strategy and terms were developed. In July 2011, the authors conducted a search of three electronic bibliographic databases (PubMed, EMBASE, and CINAHL) and gray-literature sources and databases, including the International Network of Agencies for Health Technology Assessment (INAHTA), American Medical Association Clinical Practice Improvement and Patient Safety, American Hospital Association, American Medical Association Site Search, American Nurses Association, Canadian Thesis catalog, Canadian Institute for Health Information (CIHI), DART-Europe E-theses Portal, European Health Care and Hospital Federation—Activities, Google Blog search, HealthIT.hhs.gov National Institute for Health Research (NIHR) Health Technology Assessment Programme, National Library of Medicine (NLM) Gateway, Open Gray, Proquest Dissertation Express, Scottish Intercollegiate Guidelines Network (SIGN), Surviving

Sepsis Campaign, United Kingdom Clinical Research Network Study Portfolio, Virginia Henderson International Nursing Library (VHINL), and Cochrane database for English-language articles published between 1990 and 2011. Animal studies and non-English publications were excluded.

The search contained the following medical subject headings: bacteremia; bloodstream infection; time factors; health care costs; length of stay (LOS); morbidity; mortality; antimicrobial therapy; meta-analysis; review; evaluation studies, clinical nursing research costs; cost analysis; cost-benefit analysis; nursing; diagnostic techniques and procedures; diagnosis; validation studies, evaluation studies, comparative studies; technical report; PNA-FISH; peptide nucleic acids; economics; epidemiology; outcome assessment; bacterial typing techniques; rapid molecular techniques, polymerase chain reaction (PCR); *in situ* hybridization, fluorescence; treatment outcome; drug therapy; patient care team; pharmacy service, hospital; hospital information systems; Gram stain; pharmacy service; mass spectrometry; Matrix-Assisted Laser Desorption-Ionization time of flight; phenotypic; and phenotype. The authors also included the key words cooperative behavior; agar; targeted therapy; rapid identification; rapid; Gram positive; Gram negative; reduce(ed); cost(s); pneumoslide; PBP2; tube coagulase; thermonuclease; Matrix-assisted laser desorption/ionization time of flight; MALDI TOF; blood culture; EMR; electronic reporting; call to provider; collaboration; pharmacy; laboratory; bacteria; yeast; ICU; and microbiology.

In addition to performing the electronic search, the authors made a request for unpublished quality improvement data through contacts of the expert panelists as well as e-mails to American Society for Microbiology (ASM)'s ClinMicroNet listserv and the Association of Molecular Pathology's champ listserv; in addition, a general request was posted to the Laboratory Medicine Best Practice (LMBP) Web site, now hosted at http://wwwn.cdc.gov/futurelabmedicine/default.aspx . The Web site provides instructions for submitting quality improvement data for LMBP reviews.

Screen Individual Studies

At least two independent reviewers conducted an initial screening of titles and abstracts of published articles and reviewed full articles and unpublished data submissions to assess eligibility for inclusion for each study. The initial screening of titles and abstracts was used to exclude obviously ineligible studies from a full review. A study was included if it was considered likely to provide valid and useful information and met the PICO criteria previously discussed. Specifically, these inclusion criteria required that a study evaluate a specific intervention/practice included in this review with at least one finding for a relevant outcome measure (i.e., a change in the time to targeted therapy, a change in reporting time, and others noted previously) in a format which was useful for statistical analysis. Studies that did not meet the inclusion criteria (i.e., were not considered studies or did not include a practice of interest or an outcome measure of interest) were excluded from further review.

Number of Source Documents

The authors identified a total of 1,820 nonduplicate bibliographic records and received 7 unpublished submissions covering the period of time between 1990 and July 2011. The reduction in the number of studies through the screening process is detailed in Figure 2 in the original guideline document. A total of 16 eligible studies (12 published and 4 unpublished) were considered in the review of practice effectiveness (5 published and 2 unpublished for rapid molecular techniques, 3 published and 2 unpublished for rapid molecular techniques with additional direct communication, and 4 published for phenotypic techniques).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Strength of Evidence Ratings*

The Expert Panel rates the overall strength of the body of evidence in support of the practice and it is categorized as High, Moderate, Suggestive, and Insufficient as defined.

High: Adequate volume of consistent evidence of substantial healthcare quality impact from studies without major limitations.

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Suggestive: Limited evidence of moderate healthcare quality impact from a small number of studies without major limitations; OR the quality of some studies' design and/or conduct is limited.

Insufficient: Any estimate of an effect on healthcare quality impact is too uncertain.

*These rating categories have their basis in the work of Guyatt et al.; they were modified to reflect both the quality of the evidence and effect size observed, rather than attempting to anticipate the impact of future potential evidence. The modified definitions for these categories are modeled after the U.S. Preventive Services Task Force.

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evaluate Individual Studies

Published articles and unpublished quality improvement studies retrieved for the review were screened and evaluated by at least two independent reviewers to reduce subjectivity and potential bias. Differences in study quality ratings for each study were resolved through consensus. In addition, five microbiologists, including members of the expert panel and associated members of the American Society for Microbiology reviewed and evaluated the contributing studies. For eligible articles, information on study characteristics, interventions, outcome measures, and findings of the study were extracted using a standardized form. Each study was assigned one of three quality ratings (good, fair, or poor) based on the review of study characteristics and dimensions and assigned one of three effect size ratings (substantial, moderate, or minimal/none) based on the differences in relevant outcome measures after the implementation of the practice. Details on the rating process of individual studies can be found elsewhere (see the "Availability of Companion Documents" field). Studies that did not meet the Laboratory Medicine Best Practices (LMBP) study quality criteria (i.e., those with a fair or good quality rating) were excluded. Data from published studies and unpublished quality improvement projects that passed a full review were transformed to a standardized, common metric according to Laboratory Medicine Best Practices (LMBP) methods.

Data Synthesis and Strength of the Body of Evidence (Meta-analysis Approach)

The study quality and effect size rating results from eligible individual studies for each practice were aggregated into a practice body of evidence. When possible, an overall summary effect size was calculated to translate systematic review results into one of three evidence-based recommendations (recommended, no recommendation for or against, or recommended against). Both qualitative and quantitative analyses were used to assess the effect size, consistency, and patterns of results across studies and to rate the overall strength of the body of evidence for practice effectiveness (high, moderate, suggestive, and insufficient). Criteria for these ratings are described in greater detail elsewhere (see the "Availability of Companion Documents" field).

While recommendations are based on the entire body of evidence, effect sizes were calculated for all findings providing sufficient data to estimate the expected impact of a practice. Findings based on continuous data (e.g., the time to report) were standardized using the standardized difference in means. Dichotomous findings (e.g., yes/no data, such as mortality) were summarized using the odds ratio (OR).

The quantitative analysis uses the inverse-variance weighted effect sizes from conceptually similar individual studies to produce an overall average weighted effect size (grand mean) and 95% confidence interval (CI). The grand mean is estimated using a random-effects model, and it and the contributing estimates are presented in forest plots which graphically display each study's effect size so that they can be easily reviewed and compared. The I^2 statistic estimates the percentage of variability associated with between-study differences.

In addition to there being an interest in evaluating the practices noted here, there was an interest in evaluating whether the effectiveness of rapid testing on the timeliness of the initiation of targeted therapy is related to the effectiveness of rapid testing on mortality. To do this, all effectiveness estimates of timeliness (*d*-scores) were regressed on all effectiveness estimates of mortality (log odds ratios). Although correlations do not inherently prove that causality exists, they are sufficient for estimating whether the two outcomes are likely related and determining whether there is support for the use of mortality as a proxy for timeliness.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The evidence review for this work followed the Centers for Disease Control and Prevention (CDC)'s Laboratory Medicine Best Practices Initiative (LMBP) "A-6 Cycle" systematic review methods for evaluating quality improvement practices, reported in detail elsewhere (see the "Availability of Companion Documents" field). This approach is derived from previously validated methods and is designed to evaluate the results of studies of practice effectiveness to support evidence-based best-practice recommendations. As in all A-6 cycle reviews, a systematic review question is selected. Appendix 1 in the original guideline document provides a list of the data elements of interest for the question posed for this review. Appendix 2 in the original guideline document is a glossary of terms used during this process.

Using this method, a review coordinator and staff trained to apply the LMBP methods conducts the systematic review with guidance from an expert panel. The expert panel includes seven to nine members selected for their diverse perspectives and expertise on the review topic. At least one member is an expert in evidence review methodologies.

The expert panel reviews the results of the evidence review and drafts the evidence-based best-practice recommendations, which are approved by the LMBP Workgroup. The LMBP Workgroup is an independent, multidisciplinary group composed of 15 members, 13 invited and 2 *ex officio* representatives, from federal agencies (the Centers for Medicare and Medicaid Services and the Food and Drug Administration) and with expertise in laboratory medicine, clinical practice, health services research, and health policy.

Rating Scheme for the Strength of the Recommendations

Recommendation Categories

Recommend: High or moderate for improving healthcare quality. The practice should be identified as a "best practice" for implementation in appropriate care settings, taking into account variations and applicability in implementation and/or care settings.

No recommendation for or against: Suggestive or insufficient. A potentially favorable impact on healthcare quality is not of sufficient size, or not sufficiently supported by evidence to indicate that it should be identified as a "best practice" for implementation in appropriate care settings.

Recommend against: High or moderate for adversely affecting healthcare quality. The practice should not be identified as a "best practice" for implementation because it is not likely to result in more good than harm.

Cost Analysis

Decreasing the time that it takes for bloodstream infection (BSI) microorganism identification and an antimicrobial susceptibility test (AST) result is commonly considered likely to reduce health care costs for both patients and institutions by reducing the time to appropriate targeted therapy. No economic evaluation studies that comply with guidelines for full economic evaluation were found for the rapid testing techniques evaluated in this review. Direct medical costs are impacted by the patient's length of hospital stay, repeated use of laboratory testing or other diagnostic procedures, use of broad-spectrum antimicrobials, use of targeted antimicrobial therapy, and other pharmaceutical costs.

Several studies reported a decrease in health care expenses after implementing rapid testing (see Tables A15 and A12 in Appendix 5 of the original guideline document), while others report decreased costs for antimicrobial agents and the total antifungal costs per patient. However, the cost reductions reported in these studies do not account for any additional costs associated with implementing rapid testing or costs and benefits associated with nonmedical costs (e.g., patient and caregiver time). Providing rapid testing may require additional laboratory space and additional staffing for both testing and direct communication. Other cost considerations that cannot be appropriately addressed are related to batching of tests, which occurred in most studies to make more efficient use of laboratory resources and reduce overall costs of testing.

Cost-related results should also be reported, based on quality standards for economic evaluations that would make the results meaningful and potentially generalizable and allow for comparisons across studies. A full economic evaluation is beyond the scope and the funding of this review, and the concept is being considered for future reviews. Economic evaluation is a process completely different from that of the Laboratory Medicine Best Practices (LMBP); it is worthwhile, but it does not correspond to the expertise of the LMBP team at this time and is not the purpose of the LMBP question.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The evidence-based best-practice recommendations are approved by the Laboratory Medicine Best Practices (LMBP) Workgroup. The LMBP Workgroup is an independent, multidisciplinary group composed of 15 members, 13 invited and 2 *ex officio* representatives, from federal agencies (the Center for Medicare and Medicaid Services and the Food and Drug Administration) and with expertise in laboratory medicine, clinical practice, health services research, and health policy.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Studies reviewed suggest beneficial outcomes (decreasing mortality) associated with rapid molecular and rapid phenotypic techniques with or without additional direct communication (see Table A12 in Appendix 5 in the original guideline document) and length of hospital stay in addition to reducing the time to targeted therapy in patients with bloodstream infections (BSIs). One study showed that polymerase chain reaction (PCR) surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) in a small community hospital was associated with decreasing the length of stay by 9.3% in the intensive care and critical care units in 2009 (see Table A15 in Appendix 5 in the original guideline document). Studies reviewed also indicated that the time for the laboratory to report the identification of the microorganism causing the BSI was reduced when rapid molecular or phenotypic techniques were used. Several studies also documented that there was reduced use of broad-spectrum antimicrobials when rapid molecular techniques were employed, even in the absence of additional direct communication practices. Studies using rapid molecular or phenotypic techniques with additional communication also showed reductions in the use of broad-spectrum antimicrobials. Across all of these studies, reductions in the defined daily dose of antimicrobial medications ranged from 20% to 60% with the implementation of the practice.

Potential Harms

Although not identified in the evidence base, one of several hypothetical scenarios may suggest potential harm from the use of rapid identification techniques. Harms include the lack of timely and accurate detection of a bloodstream infection (BSI) agent, despite rapid testing of positive blood culture bottles. In this scenario, the gains of the rapid testing and reporting would be nullified by the fact that the rapid intervention failed to identify the pathogen; therefore, additional laboratory costs would not be offset by a reduction in nonlaboratory costs. Risks of antimicrobial de-escalation, based on a negative rapid result, may exist during the time interval between the rapid result and the time at which the traditional culture and phenotypic methods produce a final identification and antimicrobial susceptibility test (AST) results. Furthermore, inaccurate identification of the microorganism might lead to inappropriate and ineffective changes in antimicrobial therapy, which might have significant repercussions on patient health and care if the therapy change is not warranted.

Likewise, a small proportion of blood cultures will yield more than one pathogen per bottle, resulting from infection with more than one pathogen or identification of a pathogen mixed with a typical skin contaminant. In this scenario, if rapid methods were not able to detect or discriminate between multiple pathogens, the outcome would be similar to that of the false-negative result described previously. This harm is partially mitigated by the fact that none of the assays promote rapid testing alone, without the use of a Gram stain, which can help distinguish between some pathogens in mixed infections. Furthermore, risks are limited by the subculture of the blood culture bottles, as subculture can more accurately identify mixed infections than a Gram stain alone. The implications of rapid testing methods described here may change if mixed infections become more common. Routine methods are still the definitive reference standard, and any discrepancies between a rapid method and the definitive culture result should be closely monitored; if antimicrobial therapy was inappropriately altered based on the rapid result, each instance would be reported as a potential patient safety risk.

A second harm may occur if the BSI-causing microbes that were identified by the rapid technique do not behave according to the respective institutional antibiogram. The use of an institution-specific antibiogram to guide therapy after rapid microbial identification to the genus or species level cannot account for exceptions and unforeseen mutations causing atypical susceptibility that the rapid technique cannot define. This circumstance might place patients with BSIs at risk until a final AST report is issued. Of note, this harm is implicit in all rapid methods upon which antimicrobial therapy is based and is also implicit in empirical therapy regimens.

Detection of bloodstream infections by molecular or phenotypic methods also includes the possibility of reporting results for false-positive or contaminated cultures and false-negative results due to insufficient growth in the blood culture itself. Rapid reporting of results by rapid molecular or phenotypic methods may give physicians a false sense of accuracy, causing them to overlook the basic limitations inherent in the blood culture process itself. While false-positive blood culture results are likely to be identified sooner with rapid methods and add value to differential diagnoses, false-negative results must be mitigated by clinical evidence, since some of these organisms do not grow in standard blood cultures without selective culture medium requirements or special growth conditions. False-negative results may also be due to a lack of sensitivity in the test system to detect the low density of some microorganisms.

Qualifying Statements

Qualifying Statements

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry (CDC/ATSDR).

Refer to the "Limitations" section in the original guideline document.

Implementation of the Guideline

Description of Implementation Strategy

Feasibility of Implementation

Implementation of the practices discussed in the review may be affected by specific hospital environments, laboratory settings, staff competencies, specimen volume, budget considerations, and the ability to provide active notification of test results to clinicians or pharmacists who will provide early antimicrobial interventions and appropriate therapy for patients with bloodstream infections (BSIs). Implementing any new test into a microbiology laboratory or new practice in a hospital setting often encounters resistance due to efforts to control budgets related to reagents, human resources, and other factors. Selection of an appropriate laboratory technique that best suits an institution often depends on making a business case, demonstrating potential quality outcomes or cost-effectiveness metrics.

A variety of different phenotypic and molecular techniques were utilized in the studies evaluated in this review; however, most of the studies in this review involved molecular tests performed in large university or tertiary-care centers. A number of the techniques have the capacity to identify a range of microorganisms directly from blood culture bottles determined to be positive for bacteria or yeasts (see Table A12 in Appendix 5 in the original guideline document). The hands-on times, test turnaround times, costs, and types of reagents, as well as technical skills required to perform the test, varied among these different techniques. A single peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH) test process was described and used with different PNA probes and was said to be less expensive and simpler to perform (not requiring special laboratory space) than a number of different polymerase chain reaction (PCR) procedures with which different equipment, reagents, skill levels, laboratory space, and costs were associated.

Test sensitivity and specificity are important considerations in determining feasibility for implementing a new diagnostic laboratory procedure. Studies in this review for PNA-FISH and PCR methods provided 95% or greater sensitivity and specificity for detection of the genetic targets. A potential advantage of PCR over PNA-FISH is that PNA-FISH requires at least 10^4 organisms/ml in blood for detection, while the limits of detection for PCR are typically, but not always, lower. Since microbial genetic targets are amplified in PCR, it should be able to detect organisms present at lower microbial densities. A disadvantage of PCR is related to primer specificity and competitive inhibition, which can occur when one target at higher density limits the amplification of the genetic target at lower density. There is no competitive inhibition with PNA-FISH; each microbe can freely bind with a probe on its own and can be visualized independently by fluorescence microscopy. Rapid phenotypic tests have an organism density requirement similar to that of PNA-FISH for appropriate levels of detection and accuracy.

An important aspect of any rapid testing method is to ensure that test results reach the clinician in a timely manner with specific interventions that might improve relevant patient outcomes. For the studies that implemented practices with additional direct communication, various staff that could quickly act on results and affect interventions were needed. For example, some studies required a hospital-based antimicrobial management team which consisted of a full-time infectious disease pharmacist and an infectious disease physician who devoted 25% of his/her time to antimicrobial stewardship. These types of staff members and teams may not be readily available in all hospitals.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

Buehler SS, Madison B, Snyder SR, Derzon JH, Cornish NE, Saubolle MA, Weissfeld AS, Weinstein MP, Liebow EB, Wolk DM. Effectiveness of practices to increase timeliness of providing targeted therapy for inpatients with bloodstream infections: a Laboratory Medicine Best Practices systematic review and meta-analysis. Clin Microbiol Rev. 2016 Jan;29(1):59-103. [81 references] PubMed

Adaptation

Not applicable: the guideline was not adapted from another source.

Date Released

2016 Jan

Guideline Developer(s)

American Society for Microbiology - Professional Association

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

Laboratory Medicine Best Practices - Independent Expert Panel

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Guideline Committee

Laboratory Medicine Best Practices (LMBP) Bloodstream Infection Expert Panel

LMBP Workgroup

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Financial Disclosures/Conflicts of Interest

The authors declare no conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Clinical Microbiology Reviews Web site .

Availability of Companion Documents

The following is available:

- Christenson RH, Snyder SR, Shaw CS, Derzon JH, Black RS, Mass D, Epner P, Favoretto AM, Liebow EB. Laboratory Medicine Best Practices: systematic evidence review and evaluation methods for quality improvement. Clin Chem. 2011 Jun;57(6):816-25. Available from the Clinical Chemistry Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 30, 2016. The information was not verified by the guideline developer.

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